Dynamic Random Network Model for Human Papilloma Virus Transmission

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Abstract

Human Papilloma Virus (HPV) is a widespread sexually transmitted disease which can lead to cervical cancer. Understanding the factors influencing HPV transmission has been a challenge for scientists and policy makers. We have found that previous modeling studies have not sufficiently accounted for the structural and temporal features of the sexual networks underlying HPV transmission. The aim of this study is to investigate HPV transmission processes and vaccination strategies with a dynamic relationship-based transmission model. We calibrate the epidemic model with real-world network data, and study the transmission processes with different network parameters and transmission rates. We show that a pure vaccination strategy (vaccinating only one gender) is most efficient if female-to-male and male-to-female transmission rates are equal. However, there has been recent evidence in the literature indicating that female-to-male transmission rate might be higher. Incorporating these findings into our model lead to the conclusion that male vaccination is more effective. Finally, based on our simulation results, we provide some suggestions for optimal HPV vaccination strategies.

Acknowledgements

This research project would not have been possible without the support of many people. I would like to express my gratitude to my mentor, Professor Marc Ryser who is abundantly helpful and offers invaluable assistance, support and guidance. Deepest gratitude is also due to Prof. David Kraines, who has introduced me to the PRUV Summer Research Program and given me a lot of useful advice in the academic field. I also want to convey thanks to the PRUV Program for providing the financial means. I wish to express my love and gratitude to my beloved families and friends; for their understanding and endless love, through the duration of my studies.

Contents

1 Introduction

Cervical cancer is the second most common cancer for women worldwide, with about 500 000 new cases and 250 000 deaths each year [22]. The relationship of cervical cancer and sexual activity was suspected for more than 100 years, and it was not until the 1960s that studies showing a consistent association between human papilloma virus (HPV) and cervical cancer were published [12]. Later, people have detected HPV in 99% of cervical cancers by Polymerase Chain Reaction (PCR) methodology [12], and now it is generally accepted that HPV is necessary for the development of cervical cancer [24].

Furthermore, studying cases from all over the world, HPV is also known to be associated with other types of cancers, including nearly 40% of penile cancers, 40% of vulvar and vaginal cancers, and 40% of anal cancers [24]. It has been suggested that around 26% of head and neck cancers are attributable to HPV, but prevalence varies depending on the tumor location [6].

There are more than 100 types of HPV, and about 40 types can cause genital diseases. We can also divide the 40 types of HPVs into two categories:

- Low-risk HPVs, which do not cause cancer but can cause skin warts on or around the genitals or anus and will eventually resolve over weeks or months
- High-risk or oncogenic HPVs, which can persist and cause cancer for some infected individuals. At least a dozen high-risk HPV types have been identified. HPV types 16 and 18, are responsible for 70% of HPV-caused cancers [12].

Besides its association with various types of cancers and genital diseases, we are interested in studying HPV transmission because of its subclinical and asymptomatic presentation [23]. Due to the lack of symptom, most infected individuals do not know they have HPV. Therefore, this virus can be spread easily and unconsciously during sexual encounters [23]. Studies have shown that at least 50% of men and women will acquire genital HPV infection during their lifetime [23], and HPV is currently the most common sexually transmitted disease (STD) in the United States [12]. Due to HPV's direct association with various genital diseases and cancers and its high prevalence, HPV poses a major public health concern. HPV vaccinations were first licensed in 2006 [12], and the vaccination rates vary dramatically by states: According to the C.D.C's (Centers for Disease Control and Prevention) data for 2011 [11], Rhode Island had the highest vaccination rate, with 57 percent of adolescent girls fully inoculated, followed by Vermont and South Dakota, both 50 percent. Arkansas had the lowest, 15 percent, less than half the national rate. Other states with low rates were Mississippi and Utah, at 20 percent, and Kansas, at 22 percent. Moreover, controversy about the most efficient vaccination strategy still remains. Although most research addresses the vaccination impact on female health outcomes, it has long been questioned whether optimizing HPV vaccine efficacy also requires immunizing males. In order to find the best vaccination strategy, we need to understand how HPV transmits. The subclinical and asymptomatic presentation of HPV makes its transmission process unobvious, and epidemiological research is both

time-consuming and expensive. Thus, mathematical modeling becomes an attractive tool for HPV transmission studies.

Many past studies have discussed various epidemiological models in homogeneously mixing populations. For example, Neyman [21] explained the deterministic mean-field and stochastic models for recurrent epidemics; Adler and Brunet [1] described an ODE model in which individuals can be infected simultaneously by co-circulating diseases; Castillo-Chavez et al [9] set up discrete and continuous time models with age structures. Furthermore, many researchers [7, 3, 18] investigated mathematical models for HPV transmission in homogeneously mixing populations. While homogeneously mixing population models are suitable for the spread of diseases that are transmitted through air or water, such as flu, they might not be suitable for STDs, such as HPV. According to Bearman [4], sexual network structures and partner-selection processes play an important role in HPV transmission. Past studies [20, 27] have modeled diffusion through static networks, but the time ordering of relationships in a sexual network affects STD transmission as well [19, 14]. For example, consider the 3-node network illustrated in Figure 1.

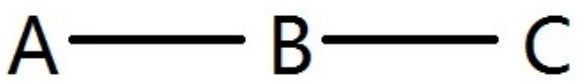

Figure 1: Static sexual network structure between A,B and C. B is in relationship with A and C, but A and C are not in a relationship.

Three people A,B and C form a static network structure as Figure 1. Assume that B is in relationship with both A and C, and A has a certain kind of STD. On the static network graph, we don't know about the timing of relationships, and both A and B, B and C have formed a sexual relationship, so A can infect C via infecting B. In the static case, C will have a chance to be infected. Next, consider that case of time-ordered relationships. If A has a sexual relationship with B before B contacts with C, B will possibly transmit the disease to C after being infected by A. On the other hand, if A has a sexual relationship with B after B contacts with C, then C cannot be infected with the disease. From this simple example, we see results of epidemic transmission with dynamic network models differ from results with static network models.

The goal of our study is to investigate HPV transmission with a dynamic random graph approach and explore optimal HPV vaccination strategies. We have found that

as most infected people became resistant, the total sum of infected people would decrease in the long run and most of the remaining infected population were persistently infected with the high-risk HPVs and had a high probability of developing cancer. From past studies, we have found various statements about HPV transmission rates, so we studied HPV vaccination strategy under different transmission dynamics. We verified that it was most efficient to vaccinate only females when transmission rates were the same across genders. But we also found that vaccinating males could be beneficial under the assumption that female-to-male transmission rates were higher.

2 Model Set-up

In order to study HPVs in a dynamic random network, we first referred to Moody's work [19] and developed a dynamic model for heterosexual partnership formation, parameterized through a 18-month study conducted by Bearman et al [4] in Jefferson High School. We chose Jefferson High School as our network model because the highest risk of HPV infection happens during adolescents between 15-19 years old [23], which is just the time for high school. This study was carried out among 429 female and 403 male teenagers and formed 474 relationships cumulatively in 18 months. Then we added the disease model to the network model by making assumptions about the initial infected population and other HPV epidemic parameters.

2.1 Bipartite Markov Chain Network Model

HPVs only transmit via sexual contact. In order to understand HPVs' transmission processes, we build a bipartite Markov Chain network model, and we make the following assumptions:

- There are N heterosexual individuals in the total population, which can be divided into N_m number of men and N_f of women, i.e. $N_m + N_f = N$.
- For the sake of simplicity, we only count heterosexual relationships in the network.
- In the beginning, everyone in the population is single.
- In the continuous time Markov process model, we assume formation of relationships are random and independent, which means that one arbitrary node can connect with any random node regardless of how many relationships the nodes are involved in at the time.
- Any two random nodes form a relationship at the rate of β.
- Random relationships break up at the rate of γ.

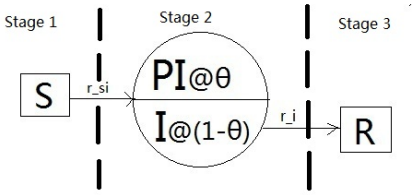

Figure 2: S-(I,PI)-R

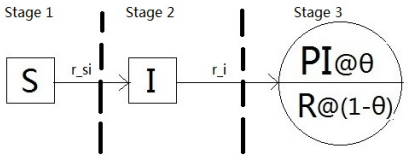

Figure 3: S-I-(R,PI)

2.2 Relationship-based Dynamic HPV Transmission Model

In the population, we denote the state of susceptible as *S*, infected (excluding persistently infected) as *I*, persistently infected as *PI*, and resistent as *R*. And we define r_{si} as the rate of transmission in an S-I or S-PI relationship, r_i as the rate of recovery, and θ as the probability of being persistently infected for one individual. We use continuous time Markov process to model HPV transmission, and Figure 2 and 3 describe two possible transmission dynamics. In Figure 2, we assume HPV persistence is an intrinsic property, which means that whether an individual is *I* or *PI* depends only on his or her immune capacity. Thus, after a susceptible individual is being infected at the rate r_{si}, we know immediately that the person has probability θ of being persistently infected, and with probability $(1-\theta)$ the person is *I* and will recover and gain resistance at the rate of r_i. We name this S-(I,PI)-R model. In Figure 3, we assume the outcome of infection is a race against time. After a susceptible individual is infected, he becomes either persistently infected with rate θr_i, or resistent with rate $(1-\theta)r_i$, depending on which event happens first. We name it S-I-(R,PI) model. In reality, neither infected people or persistently infected people have symptoms, so we don't know whether HPV persistence is an intrinsic property or a race between two events. Thus, both models are possible biologically. However, for the interest of our study, which is to explore the vaccination strategy to decrease both *I*+*PI* and *PI*, S-(I,PI)-R and S-I-(R,PI) models will give us the same result of I+PI at any time of t (the reader can refer to Appendix for detailed proof). Moreover, we know that in the long run, $\theta \cdot (I+PI)$ in the S-(I,PI)-R model equals to *PI* in S-I-(R,PI). In the S-I-(R,PI) model, the number of *PI* may still increase after the time we stopped simulation because *I* will continue change to *PI*. Our primary goal is to find a vaccination strategy that minimizes the number of *PI* in the long run. Therefore, for us, the S-(I,PI)-R model is a better choice of our HPV epidemiological study, because it will give us the final count of *PI*.

3 Parameter Estimation

3.1 Relationship Formation Rate per Week (β)

In Bearman's study [4], there are 474 relationships formed cumulatively in 18 months between 429 females and 403 males. We denote N_f as the number of females

in the population, which is 429 in this case, and N_m as the number of males in the population, which is 403. F(t) is the cumulative exponential distribution function, we know that $F(t = 18 \cdot 4 = 72) = 1 - e^{-\beta \cdot t} = \frac{474}{N_m \cdot N_f}$. Therefore, we assume $\beta = -log(1 - \frac{474}{429 \cdot 403})/72$, and we denote this value as β_B.

3.2 Relationship Break-up Rate per Week (γ)

It is hard to find an average break-up rate for teenage couples. In some populations, relationships may be more serious and lasts longer than in other populations. Therefore, we decide to compare the results between a short-term average break-up rate, which we set to be $\frac{1}{4}$ couple/week, and a long-term average break-up rate, which we set to be $\frac{1}{26}$ couple/week.

3.3 Transmission Rate (r_{si})

Different transmission rates are proposed by various past studies. After studying 25 men and 25 women at the University of Hawaii, Hernandez et al [15] state that the female-to-male transmission rate is 4.9/100 person/months, which is substantially lower than that from male to female (17.4/100 person/months).

In another study involves 179 couples in Canada (female aged 18-24 years, male aged $\geq$ 18), Burchell et al [8] conclude that there is little difference between the male-to-female (3.5 per 100 person/months) and female-to-male (4.0 per 100 person/months) transmission rates.

Widdice et al [28] also suggest that female-to-male transmission rates range from 26.8 to 187.5 per 100 person-months and male-to-female transmission ranges from 14.5 to 100 per 100 person-months. However, they also note that the intervals might be too short.

Referring to the above studies, we assume that HPV transmission rate would range from 3.5 per 100 person/months to 200 per 100 person/months, i.e. ranges approximately from 0.01 to 0.5 person per week.

3.4 Probability of Persistent Infection (θ)

We determine θ with Rodriguez's study on HPV infection [25]. The thirty-month study is conducted among 599 women in Costa Rica. In figure 4, the curve is almost flat after 30 months, so we assume no more people will further recover, and all the unrecovered people are persistently infected. The clearance percentage after 30 months is 87%, so according to our assumption, the probability of clearance is 0.87. Then $1 - \theta = 0.87$, and $\theta = 0.13$ is the probability of one infected individual being persistently infected.

3.5 Rate that a Infected Person Becomes Susceptible (r_{is})

We refer to Bogaards' [16] HPV infection model and assume $r_{is} = 0$. Figure 5 describes the SIRS epidemic model for HPV. In our model, we sum up all the transitional stage, CIN0, CIN1 and CIN2, as the infected stage, I. According to [16], the

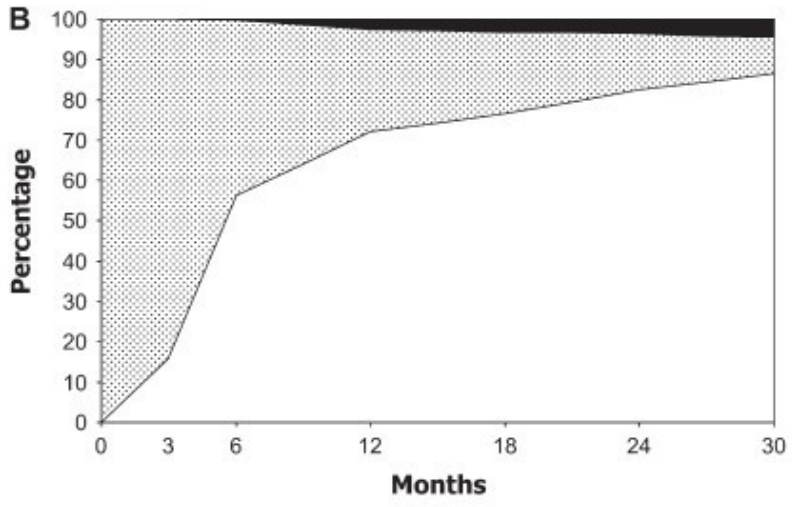

Figure 4: The clearance rate of overall HPV for people under 30 years old. The black section is the percent of persistently infected people; the dotted section are people who are currently infected, and the white section is the people who have cleared HPV [25].

infected people all get immunity after recovery, but this immunity wanes at some rate r_{rs}, which is going to be described below.

3.6 Rate that a Infected Person Becomes Resistant (r_i)

Suppose the number of recovered people stops increasing at the 30th month, and the slope is almost zero, then Figure 4 [25] resembles a cumulative exponential distribution: $F(x;r_i) = 1 - e^{-r_i x}$. Therefore, when $x = 1/r_i$, $F(x) = 1 - 1/e \approx 0.63$. To get the probability of recovery for one individual, we rescale the y axis from 0 to 0.87 to 0 to 1. From Figure 4 we see $F(x) = 0.63 \cdot 0.87 = 0.5481$ for $x \approx 6$. So r_i converted to weeks should be $\frac{1}{24}$ person per week.

3.7 Rate that a Resistant Person to Susceptible (r_{rs})

In Figure 7, Bogaards' [5] measures the rate of waning resistance for 14 types of HPV based on two studies from Netherlands, one carried out among youths below the age of 25 years in 2005 [10] and one carried out among adults aged from 18 to 69 years in 2006 [26]. Furthermore, Ortiz et al [17] study the relative prevalence of 15 types of HPV in Spain, and their result is shown in Figure 6.

We calculate the weighted average of r_{rs} by using the posterior density median for the rate of waning resistance in Figure 7 and the relative prevalence of HPV in Figure 6, using the numbers in the column under "No.(%) from general population". Figure 7 does not have HPV type 53, but Figure 6 has, so we deleted the data point

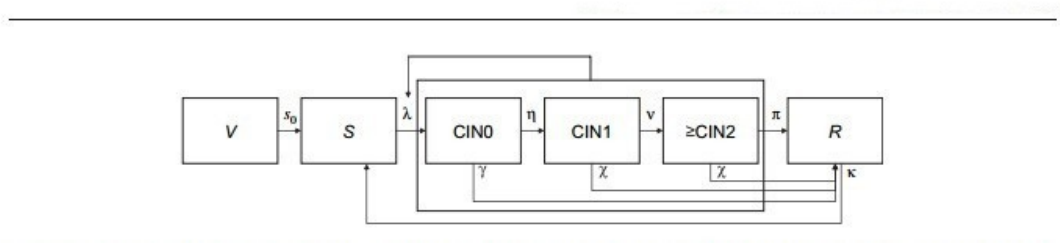

Figure 5: r_{is} is indicated by the arrow points from the big box including CIN0, CIN1, CIN2 to S, as shown in the graph, the value is zero and therefore it is not denoted by any Greek letter [16].

HPV type frequency determined by direct sequencing in oncogenic HC2 test-positive samples

HPV risk	HPV type	Total (%) no. of women	No. (%) of CSW/IPW women	No. (%) from general population	*P* value
Oncogenic	16	78 (18.4)	63 (18.7)	15 (17.0)	0.722
	18	22 (5.2)	18 (5.3)	4 (4.5)	0.507
	26	1 (0.2)	1 (0.3)	0 (0.0)	
	31	31 (7.3)	24 (7.1)	7 (8.0)	0.789
	33	16 (3.8)	12 (3.6)	4 (4.5)	0.430
	35	11 (2.6)	10 (3.0)	1 (1.1)	0.298
	39	12 (2.8)	9 (2.7)	3 (3.4)	0.467
	45	16 (3.8)	12 (3.6)	4 (4.5)	0.430
	51	11 (2.6)	6 (1.8)	5 (5.7)	0.040
	52	23 (5.4)	16 (4.7)	7 (8.0)	0.176
	53	17 (4.0)	12 (3.6)	5 (5.7)	0.263
	56	23 (5.4)	20 (5.9)	3 (3.4)	0.261
	58	28 (6.6)	24 (7.1)	4 (4.5)	0.386
	59	9 (2.1)	7 (2.1)	2 (2.3)	0.587
	66	26 (6.1)	22 (6.5)	4 (4.5)	0.490
	68	15 (3.5)	9 (2.7)	6 (6.8)	0.060
	73	2 (0.5)	2 (0.6)	0 (0.0)	0.628
	82	5 (1.2)	5 (1.5)	0 (0.0)	
Total		346 (81.4)	272 (80.7)	74 (84.1)	
Nononcogenic		33 (7.8)	30 (8.9)	3 (3.4)	
Undetermined		39 (9.2)	29 (8.6)	10 (11.4)	
β-Actin negative		7 (1.6)	6 (1.8)	1 (1.1)	
Total		425 (100.0)	337 (100.0)	88 (100.0)	

Figure 6: Relative prevalence of 15 types of HPV in Spain is shown under % from general population [17]

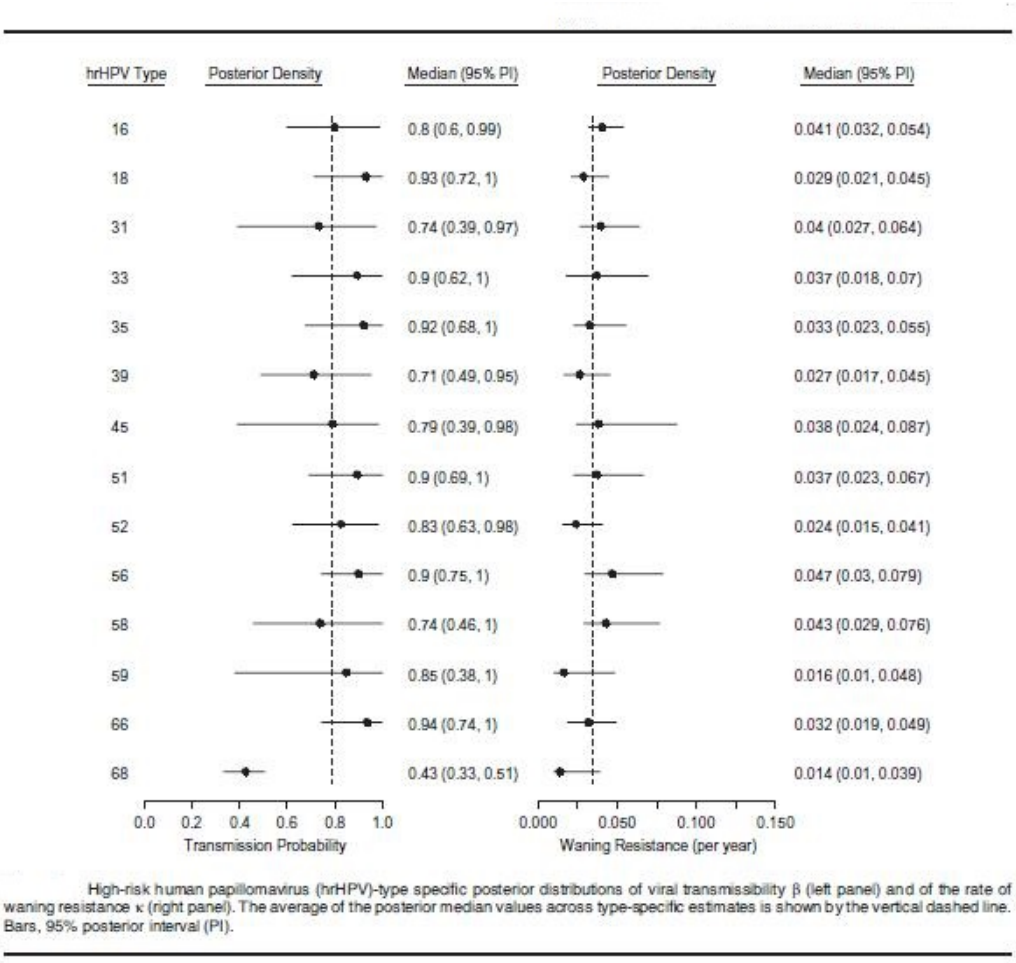

Figure 7: The numbers on left column are the medians for transmission probabilities of 14 types of HPV, and the right column are the medians for wanning resistance for 14 types of HPV [5].

of type 53 in Figure 7. Therefore, we need to rescale the percentage of "No.(%) from general population" in Figure 6 by diving each number by 0.782, which is the sum of all types' percentage except type 53. Therefore, $r_{rs} = 0.17 \cdot 0.041/0.782 + 0.045 \cdot 0.029/0.782 + 0.014 \cdot 0.068/0.782 = 0.026453$ person per year, which is $5.087 \cdot 10^{-4}$ person per week. Compared to the values of other parameters, the value of r_{rs} is negligibly small, so we approximate r_{rs} to be 0 in our model.

4 Model Simulation

To study HPV transmission processes, each time we run 50 simulations with MATLAB, calculate their average and plot the error bar on the graphs. To simplify the model, we assume the number of females and males are the same in the populations, and both equal to $\frac{429+403}{2} = 416$. We want to study how these different parameters will affect the epidemic process, so we also make the following assumptions:

- First of all, we want to simulate HPV transmission with different network parameters. As discussed in section 3.2, we choose break-up rate to be $\frac{1}{4}$ or $\frac{1}{26}$. Because relationship formation rate could depend on social factors, such as age and religion, we would also compare HPV transmission processes with different relationship formation rate, β_B and $3\beta_B$.

- According to [2], in some cases, HPV will transmit immediately when a relationship starts, so we choose a large transmission rate 1000 person/week to represent immediate transmission. Referring to Section 3.3, we also see the HPV transmission rate ranges approximately from 0.01 to 0.5 person per week. To start simple, we set the transmission rates to be 1000 person/week or 0.4 person/week for both genders.

- We choose the initial percentage of infected people in the population, p_i, to be 20% and 30%. And θ of the infected population is persistently infected, where $\theta = 0.13$ as calculated in section 3.4.

In Figure 8 and 9, we plot the sum of I and PI verses time under different sets of parameters, and we observe that most of the curves are monotonically decreasing. Only when the relationship formation rate is $3\beta_B$ and the transmission rate is 1000, the curves have a bump in our 5-year simulation. In Figure 10 and 11, we observe that the number of PI all increases. The main interest of our study is to reduce the number of PI in the population, so we will compare the number of PI under different sets of parameters.

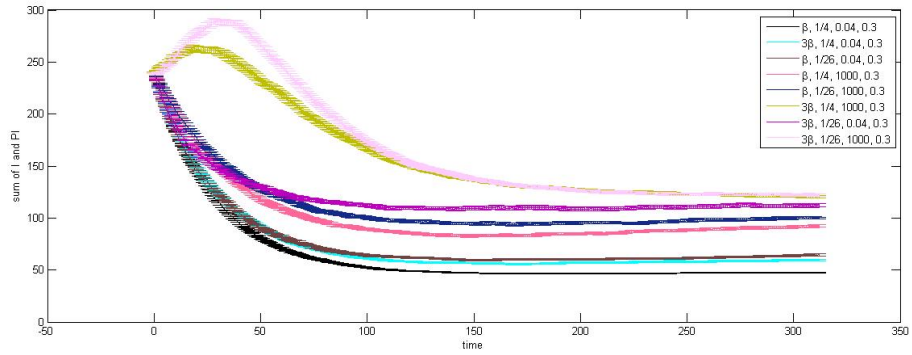

Figure 8: The number of I and PI versus time with different network parameters and initial infected is 30%. In the legend, the first column represents the value of relationship formation rate; the second column represents break-up rate; third column represents transmission rate; the rightmost column represents the percentage of initially infected population.

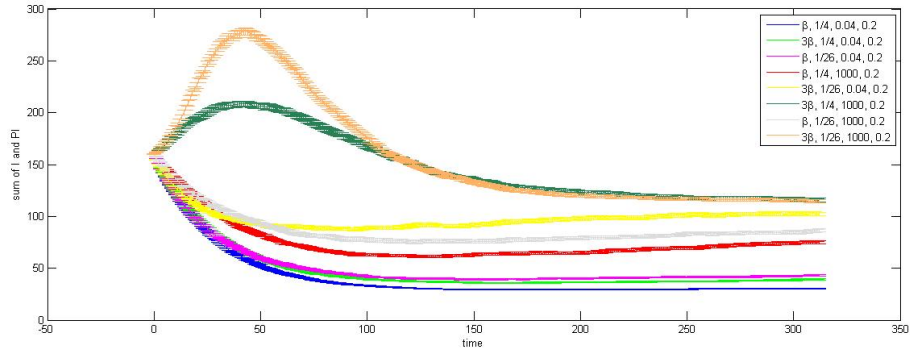

Figure 9: The number of I and PI versus time with different network parameters and initial infected is 20%. In the legend, the first column represents the value of relationship formation rate; the second column represents break-up rate; third column represents transmission rate; the rightmost column represents the percentage of initially infected population.

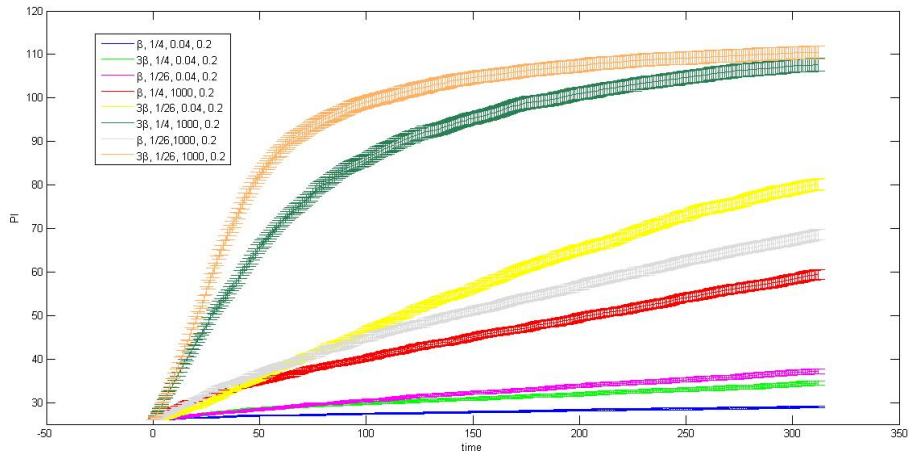

Figure 10: The number of PI versus time with different network parameters and initial infected is 20%. In the legend, the first column represents the value of relationship formation rate; the second column represents break-up rate; third column represents transmission rate; the rightmost column represents the percentage of initially infected population.

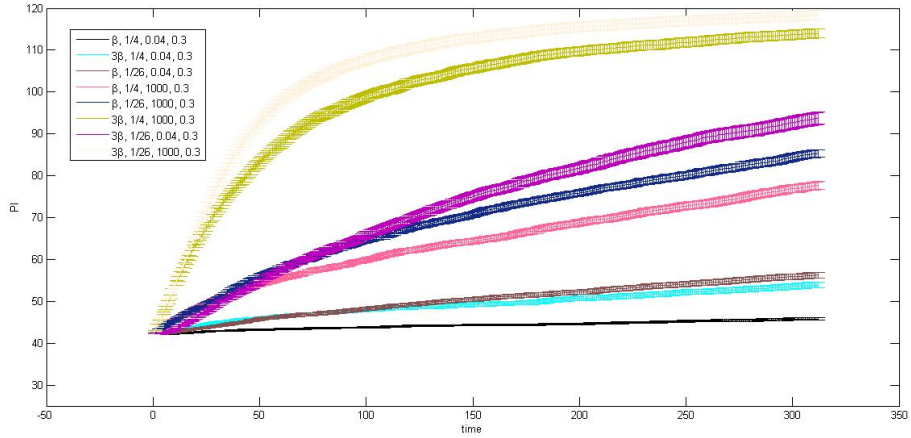

Figure 11: The number of PI versus time with different network parameters and initial infected is 30%. In the legend, the first column represents the value of relationship formation rate; the second column represents break-up rate; third column represents transmission rate; the rightmost column represents the percentage of initially infected population.

Table 1: PI with different relationship formation rates and break-up rates

(a) when transmission rate is 0.04, initial infected is 20%

β \ γ	$\frac{1}{4}$	$\frac{1}{26}$
β_B	28.98	37.18
$3\beta_B$	34.46	80.08

(b) when transmission rate is 0.04, initial infected is 30%

β \ γ	$\frac{1}{4}$	$\frac{1}{26}$
β_B	45.78	56.22
$3\beta_B$	53.86	93.62

(c) when transmission rate is 1000, initial infected is 20%

β \ γ	$\frac{1}{4}$	$\frac{1}{26}$
β_B	59.36	68.54
$3\beta_B$	107.62	110.46

(d) when transmission rate is 1000, initial infected is 30%

β \ γ	$\frac{1}{4}$	$\frac{1}{26}$
β_B	77.62	85.3
$3\beta_B$	113.98	118.32

Table 2: PI with different relationship formation rates and transmission rate

(a) when break-up rate is $\frac{1}{4}$, initial infected is 20%

β \ r_{si}	0.04	1000
β_B	28.98	59.36
$3\beta_B$	34.46	107.62

(b) when break-up rate is $\frac{1}{26}$, initial infected is 20%

β \ r_{si}	0.04	1000
β_B	37.18	68.54
$3\beta_B$	80.08	110.46

(c) when break-up rate is $\frac{1}{4}$, initial infected is 30%

β \ r_{si}	0.04	1000
β_B	45.78	77.62
$3\beta_B$	53.86	113.98

(d) when break-up rate is $\frac{1}{26}$, initial infected is 30%

β \ r_{si}	0.04	1000
β_B	56.22	85.3
$3\beta_B$	93.62	118.32

4.1 PI resulted by different parameters

From all four tables in table 1, we observe that when the relationships form at the faster rate and break up at a slower rate, more people will get persistently infected. This is because HPV transmits through relationship networks. When relationship forms at a faster rate, more couples are formed between infected and susceptible people. When the break-up rate is slower, the probability that the susceptible person is infected by his or her infected mate before they break up is also greater.

From table 2, we observe that given other parameters are the same, both larger relationship formation rate and larger transmission rate will cause more *PI* in the end of 5 years. From table 3, we observe that the network with more initially infected population would result in more *PI* after 5 years.

Table 3: PI with different relationship formation rates and initial infected

(a) when break-up rate is $\frac{1}{4}$, transmission rate is 0.04

β \ p_i	20%	30%
β_B	28.98	45.78
$3\beta_B$	34.46	53.86

(b) when break-up rate is $\frac{1}{26}$, transmission rate is 0.04

β \ p_i	20%	30%
β_B	37.18	56.22
$3\beta_B$	80.08	93.62

(c) when break-up rate is $\frac{1}{4}$, transmission rate is 1000

β \ p_i	20%	30%
β_B	59.36	77.62
$3\beta_B$	107.62	113.98

(d) when break-up rate is $\frac{1}{26}$, transmission rate is 1000

β \ p_i	20%	30%
β_B	68.54	85.3
$3\beta_B$	110.46	118.32

4.2 Introducing Vaccination to One Gender Only

We have shown in section 4.1 how different network parameters will affect the number of *PI*, now we will discuss different vaccination strategies. We decide to study how vaccination will influence populations with different network parameters and transmission rates. In section 3.2, we notice a wide range of transmission rate from 0.01 to 0.5. Thus, we will study the vaccination strategies under two situations:

- Situation 1: We choose the transmission rate $r_{si} = 0.03$, the relationship formation rate to be $5\beta_B$, and break-up rate to be $\frac{1}{52}$.
- Situation 2: We choose the transmission rate $r_{si} = 0.4$, the relationship formation rate to be $3\beta_B$, and break-up rate to be $\frac{1}{26}$.

In both cases, the initially infected population is 20% of the total population. Without loss of generality (because we can easily switch the gender in our model), we introduce vaccination to only girls in the beginning of our research. We define the percentage of female vaccination to be $p_{f,v}$, which means that at time t=0, we randomly select $p_{f,v} \cdot N_f$ girls and vaccinate them. We run simulations for $p_{f,v} = \frac{i}{10}$, when $i = 3, 4, ..., 10$. The results are shown in Figure 12-17, and in both situations, I and PI both further decrease when we vaccinate more females.

When all the females are vaccinated, it seems reasonable to believe that we have blocked most HPV transmissions and we definitely have protected all female from high-risk HPV and therefore we will directly prevent cervical cancer, which is 99% associated to the presence of HPV [12]. However, we could see that the curves of $I + PI$ in both Figure 12 and Figure 15 start to have a slight increase after reaching the minimum(in situation 1, it reaches the bottom of 68 people in the 184^{th} week and rises to 73 in the end; in situation 2, it reaches 70 people in the 138^{th} week and jumps to 72 in the end. We also notice that for $p_{f,v} = 1.0$, the slopes of S is still negative in Figure 14 and 17. This is because the females in the initially infected

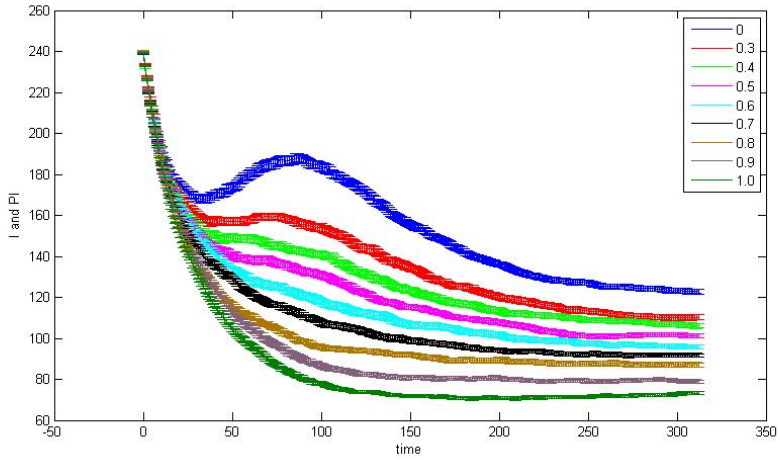

Figure 12: Situation 1: The number of infected and persistently infected people changes with time, with the vaccination percentage to be 30%-100% of the total female population. Transmission rate $r_{si} = 0.03$; relationship formation rate is $5\beta_B$; break-up rate is $\frac{1}{52}$.

population can still infect the unvaccinated susceptible males. In real life, due to HPV's asymptomatic presentation, an infected individual may get vaccinated without knowing she is already infected, and she can still transmit HPV to susceptible males.

Full vaccination can be expensive and time-consuming, so we might want to find a smaller $p_{f,v}$ that also reduce the number of I and PI drastically. According to Gertig [13], the HPV Dose-1 vaccination coverage for females in Australia is 81% for 16-17 years old and 64% for 18-19 years old. Although with larger $p_{f,v}$, the sum of I and PI are always smaller after 312 weeks, we can see that when $p_{f,v} = 0.6$ we already get promising vaccination results, the curve of $I + PI$ no longer have bumps in both Figure 12 and 15. With $p_{f,v} = 0.6$, we also used MATLAB to calculate the slope for PI during 312th week, and the result is approximately 0.0467 person/week in situation 1 and 0.0333 person/week in situation 2.

Moreover, if we only vaccinated boys, although mathematically there would not cause much difference in our model, no females would be protected by the vaccination. The initial infected boys can still transmit HPV, which is a major cause of cervical cancer, to the susceptible girls. Therefore, in reality, a full vaccination for female population is preferred over a full vaccination for male population.

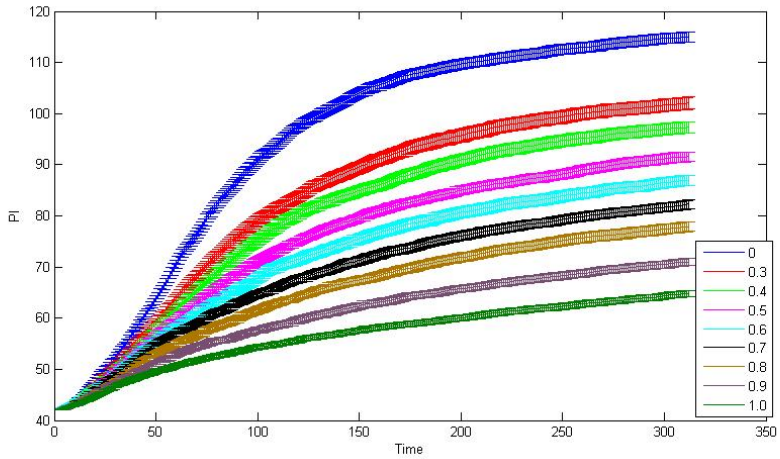

Figure 13: Situation 1: The number of persistently infected people changes with time, with the vaccination percentage to be 30%-100% of the total female population. Transmission rate $r_{si} = 0.03$; relationship formation rate is $5\beta_B$; break-up rate is $\frac{1}{52}$.

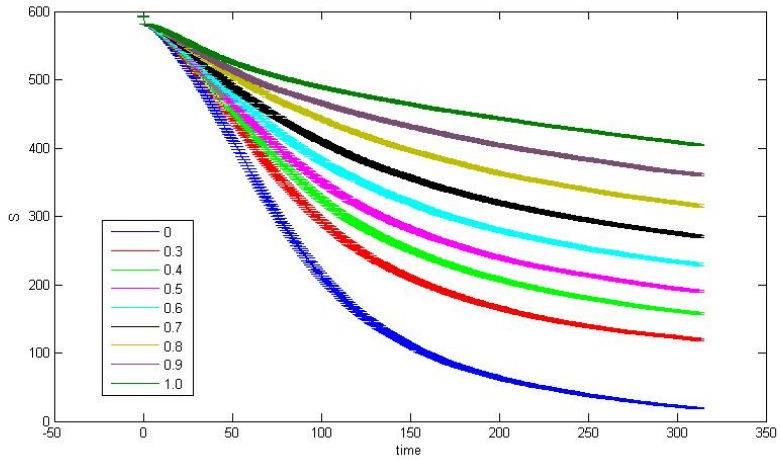

Figure 14: Situation 1: The number of susceptible people changes with time, with the vaccination percentage to be 30%-100% of the total female population. Transmission rate $r_{si} = 0.03$; relationship formation rate is $5\beta_B$; break-up rate is $\frac{1}{52}$.

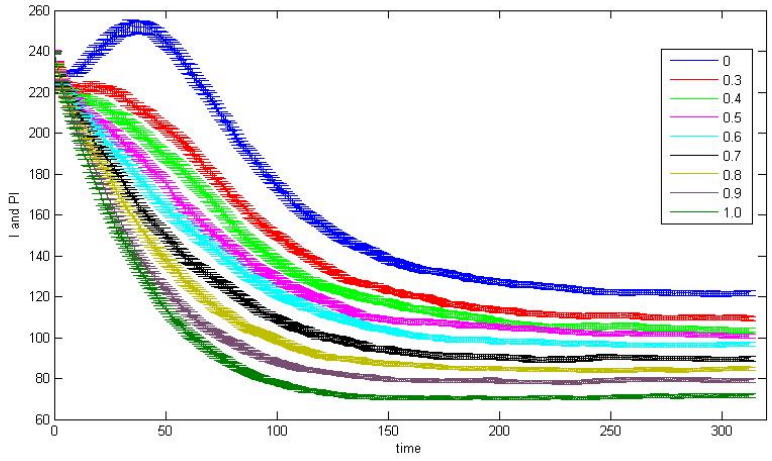

Figure 15: Situation 2: The number of infected and persistently infected people changes with time, with the vaccination percentage to be 30%-100% of the total female population. Transmission rate $r_{si} = 0.4$; the relationship formation rate is $3\beta_B$; break-up rate is $\frac{1}{26}$.

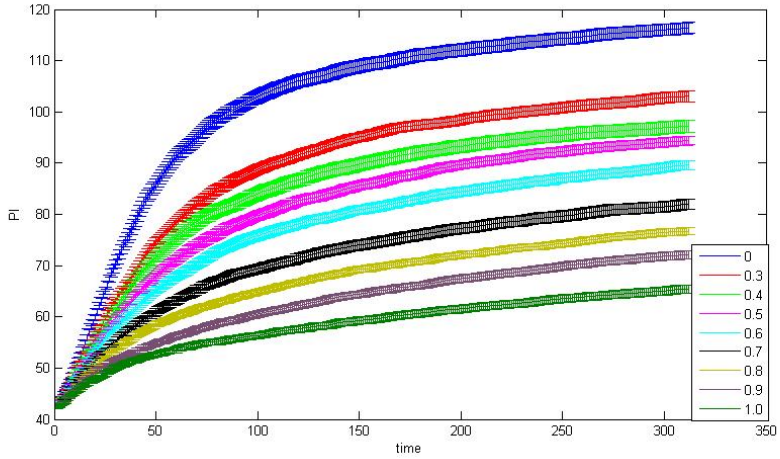

Figure 16: Situation 2: The number of persistently infected people changes with time, with the vaccination percentage to be 30%-100% of the total female population. Transmission rate $r_{si} = 0.4$; the relationship formation rate is $3\beta_B$; break-up rate is $\frac{1}{26}$.

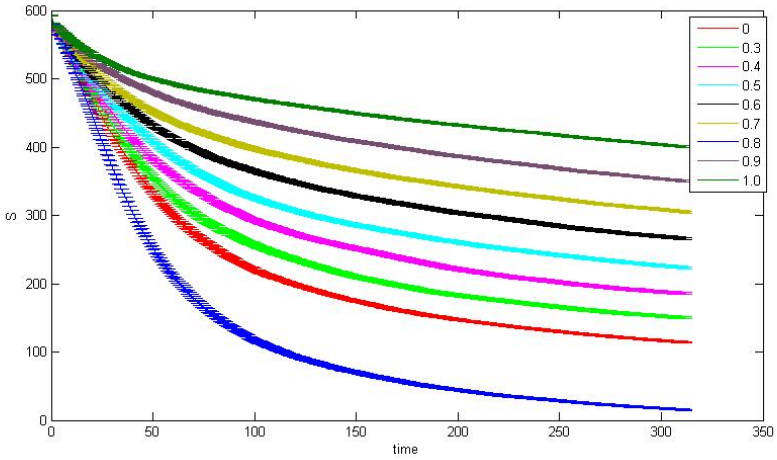

Figure 17: Situation 2: The number of susceptible people changes with time, with the vaccination percentage to be 30%-100% of the total female population. Transmission rate $r_{si} = 0.4$; the relationship formation rate is $3\beta_B$; break-up rate is $\frac{1}{26}$.

4.3 Introducing Vaccination to Girls and Boys under Same Transmission Rates

Even though females are the primary concern regarding the carcinogenic potential of HPV, infected males spread the virus as well. Here we want to study the vaccination strategy when there is little difference between the male-to-female (3.5 per 400 person/weeks) and female-to-male (4.0 per 400 person/weeks) transmission rates [8]. Because of the slight difference of the transmission rates between two genders, we assume the transmission rates are both 4.0/400 person/ week. We denote the percentage of male vaccination to be $p_{m,v}$. Suppose the cost of vaccination is the same for males and females, with the same percentage of population vaccinated, we wonder if we can get fewer *PI* by vaccinating both boys and girls. According to Gertig [13], the HPV Dose-1 vaccination coverage for females in Australia is 64% for 18-19 years old. Therefore, we chose to vaccinate 60% of the female population, which is also 30% to total population. In Figures 18-19, we see that the values of *I*+*PI* and *PI* are almost the same when we only vaccinate one gender, and *I*+*PI* and *PI* are more when we vaccinate mixtures of females and males.

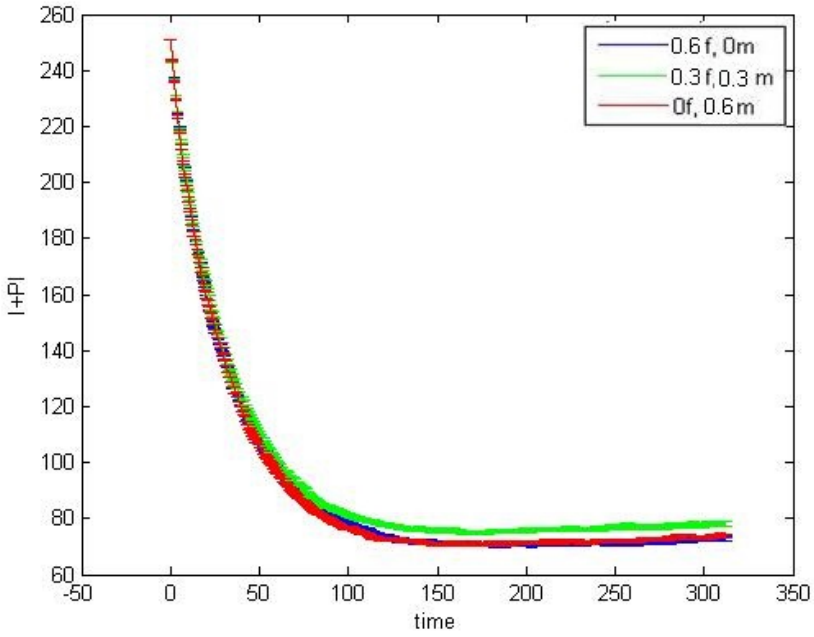

Figure 18: Sum of I and PI versus time with vaccination when relationship formation is $3\beta_B$, break-up rate is $\frac{1}{26}$, transmission rate is $4/400$, initial infected is 20%, and total vaccinated percentage is 60%. The first column of the legend is $p_{f,v}$, the second column is $p_{m,v}$.

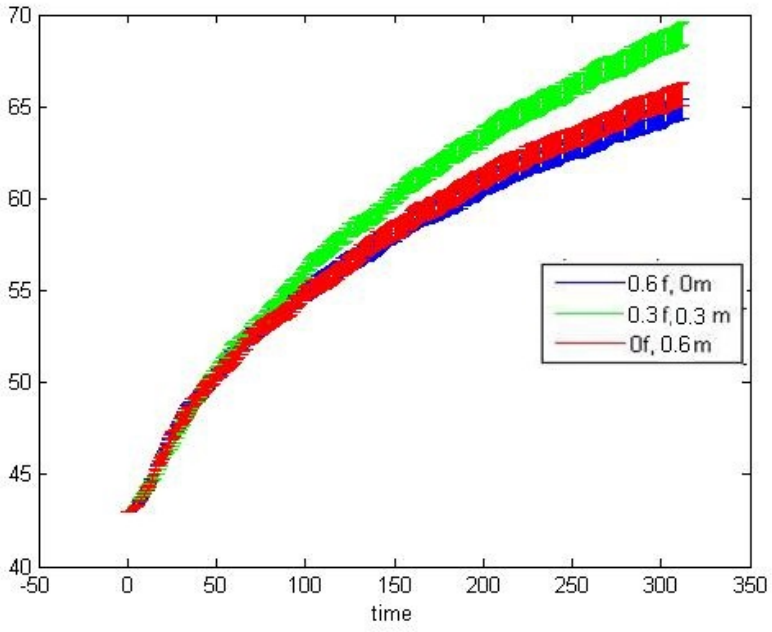

Figure 19: Number of PI versus time with vaccination when relationship formation is $3\beta_B$, break-up rate is $\frac{1}{26}$, transmission rate is 4/400,initial infected is 20%, and total vaccinated percentage is 60%. The first column of the legend is $p_{f,v}$, the second column is $p_{m,v}$.

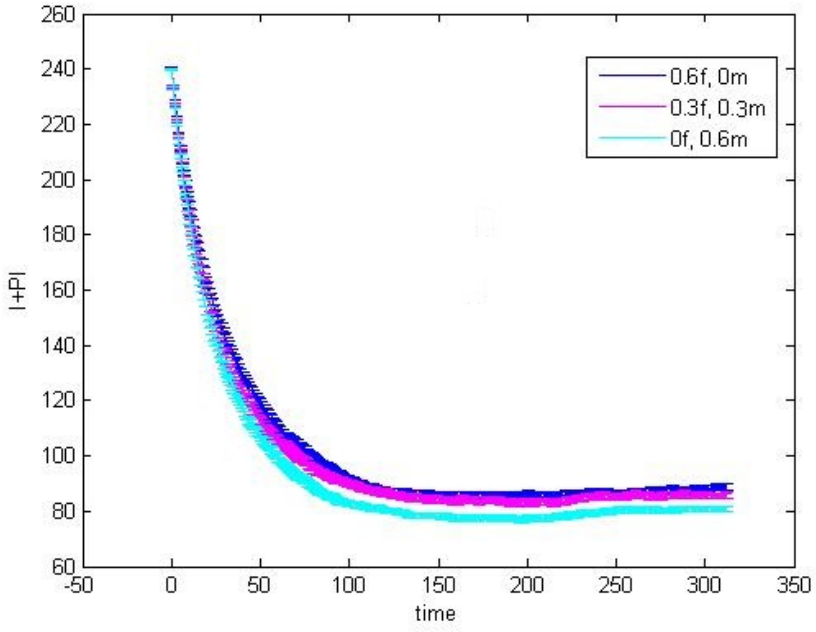

Figure 20: Number of I and PI versus time with vaccination when relationship formation is $3\beta_B$, break-up rate is $\frac{1}{26}$, and initial infected is 20%. HPV transmission rate from male to female was 4.9/400 person/weeks, and from female to male is 17.4/400 person/weeks. The first column of the legend is $p_{f,v}$, the second column is $p_{m,v}$.

4.4 Vaccination Strategy for Different Transmission Rates across Genders

In Section 4.3, we discuss about the vaccination results for the case when the transmission rates are almost equal across genders. However, according to [15], the HPV transmission rate from male to female is 4.9/400 person/weeks, and which from female to male is 17.4/400 person/weeks. Now we want to study the vaccination strategy under this circumstance. We vaccinate 30% of the total population (60% of one gender). In Figure 20 and 21, we see that no combination of $p_{f,v}$ and $p_{m,v}$ produces lower $I+PI$ and PI after 312 weeks than the strategy of vaccinating males only. This is because the transmission rate from female to male is much higher than the transmission rate from male to female. When we vaccinate more males, we have protected more of population that has a higher rate of being infected. Therefore, vaccinating more males gives us better vaccination results.

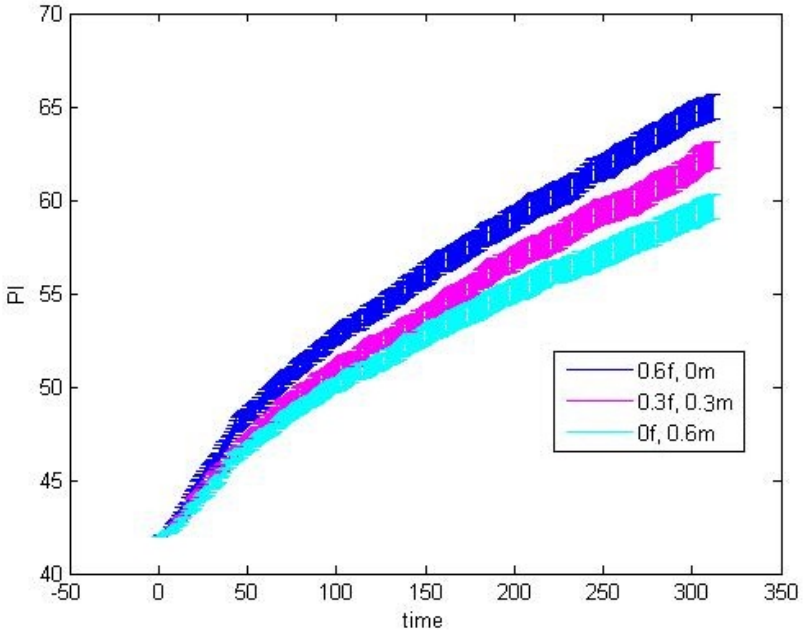

Figure 21: Number of PI versus time with vaccination when relationship formation is $3\beta_B$, break-up rate is $\frac{1}{26}$, and initial infected is 20%. HPV transmission rate from male to female was 4.9/400 person/weeks, and from female to male is 17.4/400 person/weeks. The first column of the legend is $p_{f,v}$, the second column is $p_{m,v}$.

5 Conclusion and Recommendations on HPV Vaccination

We developed a relationship-based dynamic HPV transmission model with parameters estimated from both real-life research and past HPV transmission modeling studies. We first studied how network parameters influenced the number of infected and persistently infected people in the HPV transmission process. We observed in our model that HPV transmitted faster in a network with higher relationship formation rate and slower break-up rate. If the population already had a lot of currently infected people, HPV spread more easily. Since HPV transmission rate estimates in the literature vary over a wide range [15, 28, 8], we investigated HPV epidemiology with different transmission rates. Without surprise, higher transmission rates lead to more infected people.

The impact of vaccination strategies was different in two situations. First, when the transmission rates across genders were almost equal as suggested in [8], the best vaccination strategy was to vaccinate one gender. Secondly, when the transmission rates across genders were different as suggested in [15], where the female-to-male transmission rate was much higher than the male-to-female transmission rate, vaccinating more males yielded a smaller population of infected and persistently infected individuals.

To conclude, we provide the following advice for HPV vaccination based on our study.

1. HPV vaccination should start early during pre-adolescence stage before the onset of sexual activity.

   As we see in table 3, the number of infected and persistently infected people increases as the initial infected population increases. Therefore, we need to start vaccination early before HPV spreads, i.e. vaccination should start in the pre-adolescent population.

2. HPV vaccination is highly beneficial in promiscuous populations.

   In table 1, we see that a faster relationship formation rate and a slower break-up rate will cause more persistently infected people in the population. With high relationship formation rate and low break-up rate, there is a high risk of epidemic spread, but the population can be protected with HPV vaccination.

3. The recommended vaccination percentage is 30% if not higher.

   According to our results in Section 4.2, when $p_{f,v} = 0.6$, the sum of infected and persistently infected people never increases, and the curve for persistently infected people increases with a small slope. Therefore, when we vaccinate 60% of females, we could effectively control the spread of HPV. We assume the number of females and males are the same in our population. Therefore,

we recommend that at least 30% of the total population should receive HPV vaccination.

4. When transmission rates are the same across gender, we verify the results of past studies: the optimal strategy is to vaccinate only females.

   It is shown in Section 4.3 that when transmission rates are the same, vaccinating only one gender, either male or female, will provide us the optimal result. The main purpose of HPV vaccination is to reduce the incidence of cervical cancer which is directly related to HPV infection. If we only vaccinate males, we are not protecting any females from HPV persistence and cervical cancer. Therefore, vaccinating females should be prioritized.

5. If the female-to male transmission rate is higher than the male-to-female transmission rate, vaccinating more males will further slow down HPV transmission than only vaccinating females.

   In Section 4.4, when the transmission rates across gender differ in the case that the female-to male transmission rate is much higher, we observe that vaccinating males could further decrease the infected population. Therefore, according to our model, we recommend vaccinate both females and males to prevent HPV transmission.

In our model, we only consider the case when the population has the same number of females and males, and for model simplicity, we exclude homosexual relationships. Moreover, in the process of our research, we have realized the lack of reliable experimental estimates for HPV transmission rates. From our simulation, we have observed different vaccination results caused by different sets of transmission rates. Therefore, we cannot make a confident recommendation on HPV vaccination strategy. However, we still get promising results about HPV transmission dynamics with different network parameters and transmission rates, and we also discuss which vaccination strategies yields optimal results for different sets of transmission rates.

Appendix

Theorem 1. *The sum of I and PI are the same in S-(I,PI)-R and S-I-(R,PI) model*

Sketch of proof:

- For S-I-(R,PI) model, starting at time 0, the probability for one susceptible person to become infected at time t is $p_1 = 1 - e^{-r_{si}t}$. Similarly, for S-(I,PI)-R model, at time 0, the probability for one susceptible person to become either infected or persistently infected is also $p_1' = 1 - e^{-r_{si}t}$. The probability for one person to jump from Stage 1 to Stage 2 is the same.

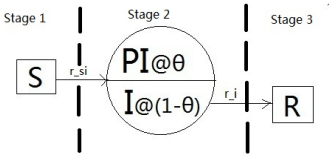

Figure 22: S-(I,PI)-R

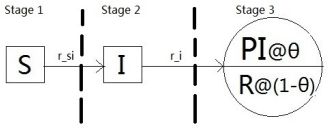

Figure 23: S-I-(R,PI)

- Then we suppose the person is at stage 2. Denote the event that the person is I or PI at time t as A,
  - For S-I-(R,PI) model, the probability of A equals to the sum of the probability that the infected person has not yet made the jump at time t and the probability that the person has jumped to PI at time t, which is $p_2 = e^{-r_i t} + (1 - e^{-r_i t}) \frac{\theta r_i}{(1-\theta) r_i + \theta r_i} = \theta - \theta e^{-r_i t} + e^{-r_i t}$.
  - For S-(I,PI)-R model, the probability of P equals to the sum of the probability that the person is persistently infected and the probability that the person is infected but has not become resistent, which is $p_2' = \theta + (1 - \theta) e^{-r_i t} = \theta - \theta e^{-r_i t} + e^{-r_i t}$.

References

[1] Frederick R. Adler and Robert C. Brunet. The dynamics of simultaneous infections with altered susceptibilities. *Theoretical Population Biology*, 40(3):369 – 410, 1991.

[2] M. Altmann. Susceptible-infected-removed epidemic models with dynamic partnerships. *Journal of Mathematical Biology*, 33:661–675, 1995. 10.1007/BF00298647.

[3] Chris T Bauch. Imitation dynamics predict vaccinating behaviour. *Proceedings of the Royal Society B: Biological Sciences*, 272(1573):1669–1675, 2005.

[4] Peter S. Bearman, James Moody, and Katherine Stovel. Chains of affection: The structure of adolescent romantic and sexual networks. *American Journal of Sociology*, 110:44–91, 2002.

[5] J. A. Bogaards, M. Xiridou, V. M. H. CoupÃľ, C. J. L. M. Meijer, J. Wallinga, and J. Berkhof. Model-Based Estimation of Viral Transmissibility and Infection-Induced Resistance From the Age-Dependent Prevalence of Infection for 14 High-Risk Types of Human Papillomavirus. *American Journal of Epidemiology*, 171:817–825, 2010.

[6] I. Borget, L. Abramowitz, and P. Mathevet. Economic burden of hpv-related cancers in france. *Vaccine*, 29(32):5245 – 5249, 2011.

[7] V. Brown and K. A. J. White. The hpv vaccination strategy: Could male vaccination have a significant impact? *Computational and Mathematical Methods in Medicine*, 11:223–237, 2010. doi:10.1080/17486700903486613.

[8] Ann N Burchell, François Coutlée, Pierre-Paul Tellier, James Hanley, and Eduardo L Franco. Genital transmission of human papillomavirus in recently formed heterosexual couples. *Journal of Infectious Diseases*, 204(11):1723–1729, 2011.

[9] C. Castillo-Chavez, H. W. Hethcote, V. Andreasen, S. A. Levin, and W. M. Liu. Epidemiological models with age structure, proportionate mixing, and cross-immunity. *Journal of Mathematical Biology*, 27:233–258, 1989. 10.1007/BF00275810.

[10] H. De Graaf, S. Meijer, J. Poelman, and I. Vanwesenbeeck. Sex below the age of 25: Sexual health of youth in the netherlands in 2005. *Delft, the Netherlands: Eburon Academic Publishers*, 2005.

[11] Centers for Disease Control and Prevention. National immunization survey (nis)-teen: Teen vaccination coverage including hpv vaccine coverage data for 2011. 2011.

[12] Centers for Disease Control and Prevention. Human papillomavirus: Epidemiology and prevention of vaccine-preventable diseases the pink book: Course textbook - 12th edition second printing. May 2012.

[13] Dorota M Gertig, Julia ML Brotherton, and Marion Saville. Measuring human papillomavirus (hpv) vaccination coverage and the role of the national hpv vaccination program register, australia. *Sexual Health*, 8(2):171–178, 2011.

[14] Mark S. Handcock and James Holland Jones. Likelihood-based inference for stochastic models of sexual network formation. *Theoretical Population Biology*, 65(4):413 – 422, 2004. Demography in the 21st Century.

[15] Zhu X Thompson P-McDuffie K Shvetsov YB Hernandez BY, Wilkens LR. Transmission of human papillomavirus in heterosexual couples. *Emerg Infect Dis [serial on the Internet]*, 2008.

[16] Helen C. Johnson, K. Miriam ElfstrÃűm, and W. John Edmunds. Inference of type-specific hpv transmissibility, progression and clearance rates: A mathematical modelling approach. *PLoS ONE*, 7(11):e49614, 11 2012.

[17] L. Muñoz E. Fernández-García J. Canals A. I. Cabornero E. Aguilar J. Ballesteros J. del Amo M. Ortiz, M. Torres and A. García-Sáiz. Oncogenic human papillomavirus (hpv) type distribution and hpv type 16 e6 variants in two spanish population groups with different levels of hpv infection risk. *J. Clin. Microbiol.*

[18] Chris T. Bauch Yonas I. Tekel Jan Medlock Lauren Ancel Meyers Alison P. Galvani Martial L. Ndeffo Mbah, Jingzhou Liu. The impact of imitation on vaccination behavior in social contact networks. *PLoS Comput Biol*, 8, 2012.

[19] James Moody. The importance of relationship timing for diffusion. *Social Forces*, 81(1):25–56, 2002.

[20] Heidi Muller and Chris Bauch. When do sexual partnerships need to be accounted for in transmission models of human papillomavirus? *International Journal of Environmental Research and Public Health*, 7(2):635–650, 2010.

[21] J. Neyman. *Proceedings of the Third Berkeley Symposium on Mathematical Statistics and Probability: Held at the Statistical Laboratory University of California, December 26-31, 1954, July and August, 1955, Contributions to Probaility Theory*. Number v. 1 in Proceedings of the Berkeley Symposium on Mathematical Statistics and Probability. University of California Press, 1956.

[22] World Health Organization. Comprehensive cervical cancer prevention and control: a healthier future for girls and women. January 2013.

[23] Jorma Paavonen. Human papillomavirus infection and the development of cervical cancer and related genital neoplasias. *International Journal of Infectious Diseases*, 11, Supplement 2(0):S3 – S9, 2007. Vaccines at the turn of the 21st century: a new era for immunization in public health.

[24] D. Maxwell Parkin and Freddie Bray. Chapter 2: The burden of hpv-related cancers. *Vaccine*, 24, Supplement 3(0):S11 – S25, 2006. HPV Vaccines and Screening in the Prevention of Cervical Cancer.

[25] Ana Cecilia RodrÃŋguez, Mark Schiffman, Rolando Herrero, Sholom Wacholder, Allan Hildesheim, Philip E. Castle, Diane Solomon, and Robert Burk. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. *Journal of the National Cancer Institute*, 100(7):513–517, 2008.

[26] Ine Vanwesenbeeck, Floor Bakker, and Susanne Gesell. Sexual health in the netherlands: Main results of a population survey among dutch adults. *International Journal of Sexual Health*, 22(2):55–71, 2010.

[27] Robert Walker, Carolyn Nickson, Jie-Bin Lew, Megan Smith, and Karen Canfell. A revision of sexual mixing matrices in models of sexually transmitted infection. *Statistics in Medicine*, 2012.

[28] Lea Widdice, Yifei Ma, Janet Jonte, Sepideh Farhat, David Breland, Stephen Shiboski, and Anna-Barbara Moscicki. Concordance and transmission of human papillomavirus within heterosexual couples observed over short intervals. *Journal of Infectious Diseases*, 2013.